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Risk factors on the development of new-onset gastroesophageal reflux symptoms : a population-based prospective cohort study : the HUNT study

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TITLE PAGE

Risk factors on the development of new-onset gastroesophageal reflux symptoms. A population-based prospective cohort study: the HUNT study

Risk factors of new-onset GERS

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WORD COUNT

3,535 words

STUDY HIGHLIGHTS

WHAT IS CURRENT KNOWLEDGE

- Gastroesophageal reflux symptoms (GERS) can severely affect health related quality of life.
- GERS are highly prevalent and the prevalence is still increasing.
- High body mass index (BMI) is associated with prevalent GERS.

WHAT IS NEW HERE

- Gain in BMI was associated with new-onset GERS, independent of BMI at baseline.
Higher gain in BMI was associated with increasing risk of new-onset GERS.
- Ever having smoked tobacco was associated with new-onset GERS.
- Tobacco smoking cessation was associated with new-onset GERS among those who gained weight upon quitting.
- Increasing age and lower education was associated with new-onset GERS.

ABSTRACT (Word count 249)

OBJECTIVES:

Gastroesophageal reflux disease (GERD) is a highly prevalent disorder. This study assessed risk factors of new-onset gastroesophageal reflux symptoms (GERS).

METHODS:

The study was based on the HUNT study, a prospective population-based cohort study conducted in 1995–1997 and 2006–2009 in Nord-Trøndelag County, Norway. All inhabitants from 20 years of age were invited. Risk factors of new-onset heartburn or acid regurgitation were examined using logistic regression, providing odds ratios (OR) and 95% confidence intervals (CI).

RESULTS:

29,610 individuals were included (61% response rate). Participants reporting no GERS at baseline and severe GERS at follow-up (new-onset GERS; $n=510$) were compared to participants reporting no complaints at both times ($n=14,406$). Increasing age (OR 1.01 per year, 95%CI 1.00–1.02) was positively whereas male sex (OR 0.81, 95% CI 0.66–0.98) and higher education (OR 0.69, 95%CI 0.56–0.86) were negatively associated with new-onset GERS. Gain in body mass index (BMI) was dose-dependently associated with new-onset GERS (OR 1.30 per unit increase in BMI, 95%CI 1.25–1.35), irrespective of baseline BMI. Previous and current tobacco smoking were associated with new-onset GERS (OR 1.37, 95%CI 1.07–1.76 and OR 1.29, 95%CI 1.00–1.67, respectively). Tobacco smoking cessation was associated with new-onset GERS among those with gain in BMI upon quitting (OR 2.03, 95% CI 1.31–3.16, with >3.5 BMI units increase).

CONCLUSIONS:

New-onset GERS were associated with increasing age, female sex, lower education, gain in BMI and ever tobacco smoking. Tobacco smoking cessation was associated with new-onset GERS among those who gained weight upon quitting.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is defined according to the Montreal classification as “a condition that develops when reflux of stomach contents causes troublesome symptoms and/or complications. (...) In population-based studies, mild symptoms occurring two or more days a week, or moderate/severe symptoms occurring more than one day a week, are often considered troublesome by patients” (1). GERD is highly prevalent in the Western world and the prevalence is still increasing (2). The treatment can be long lasting, the health expenses high, and the disease affects health related quality of life (3). Several studies have investigated prevalent gastroesophageal reflux symptoms (GERS) and related risk factors (4). Only a few studies have investigated risk factors on the development of new-onset GERS (3,5). Knowledge on the risk factors of new-onset GERS is important upon identifying persons at risk and giving evidence-based recommendations about preventive lifestyle changes. The aim of this study was to investigate the risk factors of new-onset GERS in a large population-based cohort followed prospectively over time.

METHODS

Study population

Nord-Trøndelag County, Norway, comprises approximately 135,000 inhabitants, and its residents are representative for the Norwegian population as a whole (7). The Nord-Trøndelag Health Study (HUNT) has been conducted in three consecutive surveys: HUNT1 (1984–86), HUNT2 (1995–97), and HUNT3 (2006–08). All inhabitants from 20 years of age were invited by mail. GERS were assessed in the two latter surveys. The surveys consisted of extensive questionnaires, clinical measurements, and blood samples (8). Subsequent HUNT3, non-participants were sent a mini-questionnaire (Mini-Q) by mail. Mini-Q assessed GERS as well as other health related topics. Those who participated in HUNT2 and were followed up in HUNT3 or Mini-Q were included in the present study (6).

Assessment of reflux symptoms

Participants in HUNT2 and HUNT3/Mini-Q were asked; “to what degree have you had heartburn or acid regurgitation during the previous 12 months?” followed by the response alternatives “no complaints”, “minor complaints” or “severe complaints”. Participants reporting no complaints in HUNT2 and severe complaints in HUNT3/Mini-Q were defined as having new-onset GERS, and compared to participants reporting no complaints in both HUNT2 and HUNT3/Mini-Q. Those reporting minor complaints in HUNT3/Mini-Q were excluded.

Assessment of body mass index

Trained personnel objectively measured weight and height of the participants in HUNT2 and HUNT3. In Mini-Q weight and height were self-reported. Body mass index (BMI) equals

weight in kilograms divided by height in meters squared (kg/m^2). Change in BMI was calculated as the difference in BMI between HUNT2 and HUNT3/Mini-Q and categorized into the groups: >0.5 units decrease, <0.5 units change (reference group), 0.5–1.5 units increase, >1.5–3.5 units increase, and >3.5 units increase. Based on the World Health Organization's classification for BMI; participants were stratified by normal weight (BMI <25.0), pre-obesity (BMI 25.0–29.9), and obesity (BMI ≥ 30.0) (9).

Assessment of tobacco smoking

In HUNT2 participants were asked “do you smoke?” followed by the response alternatives “never”, “previous”, or “daily”. Participants in HUNT3/Mini-Q were asked “do you smoke?” followed by the alternatives “never”, “previous”, “occasionally”, or “daily”. Based on the answer in both surveys, smoking status was categorized into the following groups: Never smokers (“never” in both HUNT2 and HUNT3/Mini-Q); previous smokers (“previous” in both HUNT2 and HUNT3/Mini-Q, or “previous” in HUNT2 and “never” in HUNT3/Mini-Q); quitters (“never” in HUNT2 and “previous” in HUNT3/Mini-Q, or “daily” in HUNT2 and “previous” in HUNT3/Mini-Q, or “daily” in HUNT2 and “never” in HUNT3/Mini-Q); and current smokers (“occasionally” and “daily” in HUNT3/Mini-Q). Ever smokers were defined as previous smokers, quitters or current smokers.

Assessment of additional covariables

All additional covariables used were assessed in HUNT3/Mini-Q with the exception of education, which was assessed in HUNT2. The additional covariables were chosen due to their potential of confounding (10). These variables were age, sex, alcohol consumption, frequency of physical exercise, and education. The participants reported their frequency of

alcohol drinking during the past 12 months and their frequency of physical exercise. The variables were dichotomized into \leq weekly or $>$ weekly alcohol consumption and $<$ weekly or \geq weekly physical exercise. The participants reported their highest level of education based on old or new educational systems in Norway, whichever relevant. For simplicity, as these levels of education also can be translated into years of education, we dichotomized education into low (≤ 12 years) or high (> 12 years).

Statistical analyses

To assess differences between those reporting no GERS and those reporting new-onset GERS, χ^2 test for categorical data and Mann-Whitney U -test for continuous data were employed. Associations between the risk factors and new-onset GERS were explored using univariable and multivariable logistic regression analyses, expressed as odds ratios (ORs) with 95% confidence intervals (95% CIs). Multivariable logistic regression models were tested for interactions, and based on these analyses the models were stratified by sex and age. A margins plot of predicted probabilities was drawn to investigate the association between age and education on the development of severe GERS. Based on this margins plot, age of 65 was set as cut-off for age strata. To estimate the proportion of severe GERS in the population attributable to change in BMI, we calculated the population attributable fraction (PAF) (11,12). The PAF was calculated according to the following formula:

$$\text{PAF} = 100 \times \frac{p_{ex}(OR - 1)}{p_{ex}(OR - 1) + 1}, \text{ where } p_{ex} \text{ represented the prevalence of the exposure (change in}$$

BMI) in the population under study and OR the adjusted OR of the risk factor. Individuals with missing data were left out from the analyses. Hosmer-Lemeshow test for goodness of

fit was applied on all regression models. All analyses were performed using Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.

Study Approval

This study was approved by “The Regional Committee for Medical and Health Research Ethics, Central Norway” (ID: 2012/1290 4.2009.328). All participants signed a written consent.

RESULTS

Participation

The participation has previously been reported in detail (13). To summarize, in HUNT2 (1995–97) and HUNT3/Mini-Q (2006–09), 58,864 (64% response rate) and 44,997 (49% response rate) individuals reported their degree of GERS, respectively. Among these 29,610 individuals participated in both surveys, corresponding to 61% successfully followed up, after excluding 10,535 participants who had died or were no longer resident in the county at the time of HUNT3/Mini-Q (non-eligible for follow-up). Mean follow-up time was approximately 11 years. When comparing participants successfully followed up in HUNT3/Mini-Q to all participants in HUNT2 the former group was characterized by lower age, more women, fewer smokers, a lower proportion who did not exercise weekly, and higher education (6). There were no differences in GERS, BMI, or alcohol consumption. Of the 20,310 participants reporting no complaints in HUNT2, 510 reported severe complaints (new-onset GERS) in HUNT3/Mini-Q and 14,406 reported no complaints (**figure 1**).

Individuals reporting new-onset GERS at follow-up were more likely to be women, have higher BMI, being ever smokers, doing less physical exercise, and have lower education, than individuals reporting no complaints in HUNT3/Mini-Q (**table 1**). Women had higher increase in BMI during follow-up than men (mean 1.14 and 0.99, respectively), and more women than men had weight gain of 1.5–3.5 BMI units (41.3% vs. 36.9%) and >3.5 BMI units (14.2% vs. 8.5%).

Main analysis

New-onset GERS was negatively associated with male sex and higher education; whereas, it was positively associated with increasing age, increase in BMI during follow-up and ever

smoking (**table 2**). More than weekly physical exercise was negatively associated with new-onset GERS in the univariable analysis, but the association was not maintained after adjustments for the other variables (**table 2**). Alcohol consumption did not show any association with new-onset GERS (**table 2**).

Sub-analysis: body mass index

A dose-response relationship between increasing BMI categories and risk of new-onset GERS was demonstrated (p for trend <0.001 ; **figure 2a**). Adjusted OR for new-onset GERS was 1.77 (95%CI 1.28-2.45) and 4.91 (95%CI 3.54-6.81) among those with an increase in BMI >1.5 – 3.5 and >3.5 units, respectively (**figure 2a**). PAF was estimated to be -5.9% among participants with ≥ 0.5 units decrease in BMI, 6.9% among those having 0.5–1.5 units increase, 17.6% among those having >1.5 – 3.5 units increase, and 31.8% among those having >3.5 units increase.

When stratifying by BMI at HUNT2, a BMI increase of >3.5 units in the normal weight group (BMI <25.0) and a BMI increase of >1.5 – 3.5 or >3.5 units in the pre-obese group (BMI 25.0–29.9) were associated with new-onset GERS (**figure 2b** and **2c**). In the obese group (BMI ≥ 30) a similar trend was observed (**figure 2d**). There was a dose-response relationship between increasing BMI and the risk of new-onset GERS in all strata (p for trend ≤ 0.003).

The adjusted OR of new-onset GERS per unit increase in BMI at HUNT3/Mini-Q was 1.10 (95% CI 1.08–1.12).

Sub-analysis: tobacco smoking

In analyses stratified by tobacco smoking status, change in BMI between HUNT2 and HUNT3/Mini-Q had no substantial influence on the risk of new-onset GERS in previous

smokers (quitting smoking before baseline in HUNT2) or current smokers (**figure 3a and 3c**). However, smoking cessation (quitting smoking between baseline in HUNT2 and follow-up in HUNT3/Mini-Q) was associated with new-onset GERS among those with >1.5-3.5 and >3.5 units increase in BMI (OR 1.71, 95% CI 1.04-2.79 and OR 2.03, 95% CI 1.31-3.16, respectively; **figure 3b**). Those exposed to smoking cessation and >3.5 units increase in BMI, had a lower BMI at baseline than never smokers (mean 25.0 and 26.1, respectively), but had a higher mean BMI increase than the never smokers (mean 5.15 and 4.98, respectively).

Sub-analysis: education, sex and age

Education interacted with age and sex. There was a stronger association between new-onset GERS and low education among the younger participants (<65 years) than the older participants (≥65 years), and among women than men (**supplementary figure 1**).

Increasing age was positively associated with new-onset GERS for both sexes <65 years, but there was no such association in the group ≥65 years (**supplementary table 1**). Increase in BMI was associated with new-onset GERS for both sexes and all ages, except for men ≥65 years (**supplementary table 1**). For men of ≥65 years 4.2% ($n=75$) had a gain in BMI >3.5 units, which was low compared to women of ≥65 years (7.3% [$n=139$]).

DISCUSSION

In this population-based prospective cohort study with approximately 11 years follow-up there was a dose-dependent association between gain in BMI and new-onset GERS, irrespective of the participant's BMI at baseline. Ever smoking was positively associated with new-onset GERS. Smoking cessation was also positively associated with new-onset GERS, however, only in those who gained BMI upon quitting. Women had increased risk of new-onset GERS compared to men. The risk of new-onset GERS increased with lower level of education and increasing age.

The population-based design and the large study sample are major strengths of this study that increases power, decreases risk of chance findings, helps diminish selection bias, and facilitate subgroup analyses. The prospective design minimizes recall bias. The population of Nord-Trøndelag County is a stable population which is representative of the Norwegian population at large, with the exceptions of a slightly lower average income and absence of a large city (7,14).

One weakness of this study is that it was conducted before the Montreal consensus and did not utilize the definition (1). However, the Montreal definition states that "moderate/severe symptoms occurring more than one day a week, are often considered troublesome by patients" and in a validation study succeeding HUNT2 and in the Mini-Q, 95 and 98% of the participants who reported severe GERS stated "at least weekly symptoms", respectively (15). Thus, most participants in this study meet the Montreal criteria. Participants reporting minor complaints were left out of all analyses, because their complaints represented sporadic, less than weekly symptoms in 75 and 69%, respectively (13,15). To better identify participants with symptoms caused by reflux, rather than non-specific complaints, a definition of

heartburn and acid regurgitation could have been explained to the participants. Thus, some participants reporting GERS in this study might not have true GERD.

Self-measured height and weight in Mini-Q ($n=1,696$ [11.3%]) is a limitation of this study introducing potential information bias and underreporting of gain in BMI (16). However, this will result in an underestimation of the association between gain in BMI and new-onset GERS, attenuating the positive association.

The Norwegian Prescription Database was established in 2004 and the participant's consumption of anti-reflux medication in HUNT2 could not be assessed. Thus, some individuals with GERD could have been categorized as having no GERS at baseline due to treatment. However, studies have found that among patients with GERS, 63.4% report current symptoms and 72% report recent symptoms despite being on anti-reflux medications (17,18). This held together with the fact that many patients with GERD are instructed in an intermittent on-demand treatment regime based on symptoms and the questionnaire's 12 months recall period, indicates that the majority of participants with prevalent GERS would have reported minor or severe GERS at HUNT2.

Information on education was obtained in HUNT2 and was not assessed in HUNT3/Mini-Q. Earlier findings on socioeconomic status (SES) and GERS from HUNT1 and HUNT2, indicate that there should not be any difference on whether this information is collected in HUNT2 or HUNT3/Mini-Q (19).

Non-participation in HUNT3 has been validated, and was associated with high age, male sex, low SES, and chronic diseases (20). It is reasonable to assume that the same differences were present at inclusion in HUNT2. In our study, those participating in HUNT2 had essentially similar demographic and baseline characteristics as those successfully followed

up in HUNT3/Mini-Q. After excluding those participants who had died or moved from the county, 61% was successfully followed up, which is considered adequate (21).

One could propose that if the whole background population were included in HUNT2 and followed up successfully, more individuals of old age, smokers, and low education would have participated, making stronger estimates with more narrow confidence intervals possible (20,22). Especially for the oldest participants, more precise estimates could have been made. In the multivariable analyses, 989 (6.6%) of the participants had missing values. Because this relatively low number, no further corrections were made to assess missing values, assuming no substantial influence on the results. In HUNT2 and HUNT3/Mini-Q, 570 and 237 participants reported to be pregnant, respectively. This study did not assess pregnancy. However, pregnancy did not change the cumulative incidence of GERS in this study population (13). We cannot rule out residual confounding due to unmeasured factors. To our knowledge, only one Danish and one UK study have assessed risk factors on development of new-onset GERS (3,5). The Danish study comprised participants of 40–65 years of age, and found new-onset GERS to be associated with high BMI at follow-up, low education, and consumption of antacids. The UK study comprised participants of 50–59 years of age and had a low follow-up rate (40.7%), but found new-onset GERS to be associated with high BMI at follow-up and low quality of life at baseline.

The present study suggests a dose response relationship between gain in BMI and new-onset GERS, independent of the participants BMI at baseline. No study has earlier described such an association. PAFs calculated in this study suggest that gain in BMI, especially >3.5 units increase, attributes to a large proportion of the cases with new-onset GERS.

In agreement with previous studies, the present study found no association between new-onset GERS and alcohol consumption. We note that alcohol consumption in this study was

lower than in the two other studies, representing the consumption in the Norwegian population (23).

Several population-based studies have found a positive association with tobacco smoking and prevalent GERS (4). Our study confirms the association with new-onset GERS. The present study also demonstrated a relationship between tobacco smoking cessation and new-onset GERS, which corresponds to an earlier finding assessing previous smokers (24). However, when stratifying for gain in BMI during follow-up, these participants had a notably higher gain in BMI compared to the other participants. This probably explains the association between tobacco smoking cessation and new-onset GERS, and corresponds to earlier findings on smoking cessation and substantial weight gain (25). This implies that weight gain must be avoided if smoking cessation should be effective as a lifestyle treatment of GERS, previously shown in the HUNT study (26).

Unlike the Danish and UK studies, we found a slight association with age on new-onset GERS (OR 1.01 per year, 95%CI 1.00–1.02). The association is of minor importance from year to year, but over decades the association gets more important. Age showed association with new-onset GERS in participants <65 years, but no association with age was found in participants ≥65 years of age. The number of participants in the strata of women ≥65 years and men ≥65 years was low ($n=1,632$ and $n=1,656$, respectively), and this reduces power to detect minor associations. Anyhow, these findings corresponds to an earlier study where age was not associated with new-onset GERS in participants >69 years of age (24). The reason for not finding any association between gain in BMI on new-onset GERS among men ≥65 years seems to be due to the low number of individuals along with few participants with a substantial gain in BMI compared to the three other strata.

Difference between the sexes found in our study seems to be due to a higher weight gain among women than men. Also, more men had prevalent reflux in HUNT2 and thereby were excluded from the present study (13). The present study suggests that education as a measure of SES has varying influence on new-onset GERS on the wide age span of this study sample. In the population <65 years of age, low level of education was associated with new-onset GERS among women and the same trend was seen for men. However, there was no such association between new-onset GERS in the population ≥ 65 years. In the population ≥ 65 years, higher education was less common and thus education is a suboptimal measure of SES in this subpopulation.

CONCLUSION

In this large prospective population-based cohort study increasing age, female sex, increase in BMI, ever tobacco smoking, and low level of education were associated with new-onset GERS. Because of an increase in BMI after smoking cessation, new-onset GERS was associated with smoking cessation as well. Weight gain attributed to a considerable part of new cases of GERS, independent of weight at baseline. Our findings enhance that avoiding weight gain is an important preventive measure of GERS.

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CONFLICT OF INTEREST

Guarantor of the article: Andreas Hallan, BSc Med.

Specific author contributions: A.H., M.B., J.M.-H., and E.N.-J. have provided substantial contributions in planning and conducting the study, interpreting data, drafting manuscript, and have approved the final draft submitted; K.H. has provided substantial contributions in planning and conducting the study, collecting and interpreting the data, drafting the manuscript, and he has approved the final draft.

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Potential competing interests: None.

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FIGURE LEGENDS

Figure 1. Participants for the assessment of new-onset GERS; GERS, gastroesophageal reflux symptoms; HUNT, Nord-Trøndelag Health Study.

Figure 2. Odds ratios (OR) with 95% confidence intervals (95% CI) for development of new-onset gastroesophageal reflux symptoms (GERS) by change in body mass index (BMI) during follow-up HUNT2–HUNT3/Mini-Q, stratified by weight at baseline HUNT2; adjusted for age, sex, tobacco smoking, alcohol consumption, physical exercise, and education.

Figure 3. Odds ratios (OR) with 95% confidence intervals (95% CI) for development of new-onset gastroesophageal reflux symptoms (GERS) by change in body mass index (BMI) during follow-up HUNT2–HUNT3/Mini-Q, stratified by tobacco smoking status ; adjusted for age, sex, alcohol consumption, physical exercise, and education.